


ORIGINAL RESEARCH

# Pharmacotherapy in the Management of Anxiety and Pain During Acute Coronary Syndromes and the Risk of Developing Symptoms of Posttraumatic Stress Disorder

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**BACKGROUND:** Benzodiazepines and morphine are given during acute coronary syndromes (ACSs) to alleviate anxiety and pain, and  $\beta$ -blockers may also reduce pain. ACS may induce posttraumatic stress disorder (PTSD) symptoms (PTSS). When taken during trauma other than ACS, benzodiazepines increase the risk of PTSS, but it is unknown if benzodiazepines increase the risk of PTSS in ACS. We examined the effects of drug exposure during ACS on the development of PTSS.

**METHODS AND RESULTS:** Study participants were 154 patients with a verified ACS. Baseline demographics, clinical variables, and psychological measures were obtained through a medical history, through a psychometric assessment, and from patient records, and used as covariates in linear regression analysis. Three months after ACS, the severity of PTSS was assessed with the Clinician-Administered PTSD Scale. During ACS, 37.7% of patients were exposed to benzodiazepines, whereas 72.1% were exposed to morphine and 88.3% were exposed to  $\beta$ -blockers, but only 7.1% were exposed to antidepressants. Eighteen (11.7%) patients developed clinical PTSD. Adjusting for all covariates, benzodiazepine use was significantly associated with the Clinician-Administered PTSD Scale total severity score (unstandardized coefficient B [SE], 0.589 [0.274]; partial  $r=0.18$ ;  $P=0.032$ ) and the reexperiencing subscore (B [SE], 0.433 [0.217]; partial  $r=0.17$ ;  $P=0.047$ ). Patients exposed to benzodiazepines had an almost 4-fold increased relative risk of developing clinical PTSD, adjusting for acute stress disorder symptoms (odds ratio, 3.75; 95% CI, 1.31–10.77). Morphine,  $\beta$ -blockers, and antidepressants showed no predictive value.

**CONCLUSIONS:** Notwithstanding short-term antianxiety effects during ACS, benzodiazepine use might increase the risk of ACS-induced PTSS with clinical significance, thereby compromising patients' quality of life and prognosis.

**REGISTRATION:** URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT01781247.

**Key Words:** cardiovascular disease ■ pharmacotherapy ■ posttraumatic stress disorder ■ psychological stress ■ risk factor

Coronary care unit staff has long been aware that the average patient with an acute coronary syndrome (ACS) is anxious at the time of hospital admission,<sup>1</sup> with the mean state anxiety level in patients doubling that of a normal reference group.<sup>2</sup> Within 48 hours of ACS onset, almost 50% of patients report anxiety,<sup>3</sup> and about half of these have high levels

of anxiety.<sup>4,5</sup> Guidelines of the European Society of Cardiology recommend the use of a mild tranquillizer, usually a benzodiazepine, for the treatment of anxious patients presenting with ST-segment-elevation myocardial infarction (STEMI).<sup>6</sup>

Two major reasons for acute anxiety during ACS are fear of dying and pain.<sup>1</sup> Clinically significant fear of

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## CLINICAL PERSPECTIVE

### What Is New?

- Patients receiving benzodiazepines in the setting of an acute myocardial infarction had more severe infarction-induced posttraumatic stress symptoms of clinical significance at 3 months than patients not prescribed benzodiazepines.
- For individual posttraumatic stress symptom clusters, an association with benzodiazepine use was particularly observed for reexperiencing aspects of myocardial infarction, for instance in thoughts or dreams.
- The effect was independent of demographic factors, clinical and psychosocial variables, and concomitant exposure to morphine,  $\beta$ -blockers, and antidepressants.

### What Are the Clinical Implications?

- Although benzodiazepines provide rapid relief from anxiety during myocardial infarction, they could contribute to posttraumatic stress in the longer-term.
- In the setting of an acute myocardial infarction, clinicians should prescribe benzodiazepines only with a clear indication, knowing that infarction-induced posttraumatic stress is associated with impaired quality of life and prognosis.
- As our findings are not from a randomized controlled trial, it is possible that patient characteristics leading to posttraumatic stress and the prescription of benzodiazepines were similar.

## Nonstandard Abbreviations and Acronyms

<b>ASD</b>	acute stress disorder
<b>CAPS</b>	Clinician-Administered Posttraumatic Stress Disorder Scale
<b>GRACE</b>	Global Registry of Acute Coronary Events
<b>MI-SPRINT</b>	Myocardial Infarction–Stress Prevention Intervention
<b>PTSS</b>	posttraumatic stress disorder symptoms

dying and acute distress occur in 2 of 3 patients during ACS and are strongly correlated with chest pain.<sup>7</sup> Intravenous opioids are usually necessary for effective pain relief,<sup>6</sup> but the combination with benzodiazepine can reduce the use of morphine and its adverse effects.<sup>8,9</sup> Benzodiazepines rapidly relieve the anxiety triggered by ischemic chest pain, thus counteracting a vicious cycle of pain, anxiety, and distress, associated with sympathetic activation causing increased

workload of the heart.<sup>10</sup> Intravenous  $\beta$ -blockers, applied to reduce malignant ventricular arrhythmias in patients with ACS,<sup>6</sup> have also marked pain-relieving effects.<sup>11</sup> Patients often receive a combination of benzodiazepine, morphine, and  $\beta$ -blockers, although it is unknown how these drugs are to be combined to manage anxiety and pain during ACS most effectively.<sup>12</sup>

Induced by the traumatic experience of ACS as a life-threatening disease,<sup>13</sup> patients develop posttraumatic stress disorder (PTSD) in 4% and clinically significant PTSD symptoms (PTSS) in 12% after 1 to 12 months.<sup>14</sup> Typical PTSS may include reexperiencing aspects of ACS in thoughts or dreams, avoidance of activities that remind of ACS, and hyperarousal symptoms.<sup>15</sup> Notwithstanding their short-term antianxiety effects, benzodiazepines could be a risk factor for the development of ACS-induced PTSS, seen in critical illness survivors exposed to benzodiazepines in the intensive care unit.<sup>16</sup> Moreover, benzodiazepines increase the risk of developing PTSD at least 2-fold in patients who experience trauma, because benzodiazepines could interfere with the acute physiological stress response and memory-related processes necessary to cope with PTSS.<sup>17</sup> On the other hand, a decrease in both pain and fear conditioning could explain less severe PTSS at follow-up in civilian and military patients who received morphine within hours of trauma.<sup>18,19</sup> Pain and fear of dying during ACS are risk factors for the development of PTSS,<sup>20,21</sup> but effects of morphine use on ACS-induced PTSS have not yet been investigated.<sup>13</sup> There is currently no meta-analytic evidence that antidepressants or the  $\beta$ -blocker propranolol prevents the development of PTSS after a traumatic event.<sup>22,23</sup> However, one previous study observed lowered PTSS at 1 month in patients with  $\beta$ -blockers during emergency department evaluation for ACS.<sup>24</sup>

On the basis of the current evidence, the primary aim of our observational study was to test the hypothesis that exposure to benzodiazepines during ACS is associated with increased severity of PTSS 3 months later. Our secondary aim was to explore effects of morphine,  $\beta$ -blocker, and antidepressant exposure during ACS on ACS-induced PTSS at 3 months.

## METHODS

### Study Participants and Design

The data that support the findings of this study are available from the corresponding author on reasonable request. The participants of this study were enrolled in the MI-SPRINT (Myocardial Infarction–Stress Prevention Intervention) randomized controlled trial aimed at preventing the development of ACS-induced PTSS through an early behavioral intervention.<sup>25</sup> We did not include the intervention in the current analysis

because it showed no effect on interviewer-rated PTSS at 3-month follow up, the primary end point of the present study, which was assessed in 154 patients.<sup>26</sup> We included patients aged  $\geq 18$  years with verified STEMI or non-ST-segment-elevation myocardial infarction (MI), stable circulation, and high peritraumatic distress, defined by numeric rating scores (range, 0–10) of  $\geq 5$  for pain plus  $\geq 5$  for fear of dying and/or helplessness during ACS.<sup>27</sup> We excluded patients with emergency coronary artery bypass grafting, diseases likely to cause death within 1 year, limited orientation, cognitive impairment, current severe depression, according to the cardiologist's medical history, suicidal ideations in the previous 2 weeks, and insufficient German skills; or when they participated in another randomized controlled trial. The local ethics committee approved the trial protocol, which was registered under ClinicalTrials.gov (NCT01781247). All patients provided written informed consent.

## Baseline Measures

Baseline measures were obtained in the coronary care unit through a structured medical history, through psychometric assessment, and from patient records, including information on drugs to which patients were exposed during ACS. For benzodiazepines, opioids, and  $\beta$ -blockers, “drug exposure” referred to any use of these drugs during the short-term treatment phase of ACS. For antidepressants, “drug exposure” referred to the current use of antidepressants at the time of ACS. As a measure of socioeconomic status, we categorized educational level as high (university graduation, including applied sciences; or high school graduation/matura), medium (apprenticeship or vocational school), or low (lower than apprenticeship or vocational school).<sup>28</sup> We used the GRACE (Global Registry of Acute Coronary Events) score to estimate the cumulative mortality/recurrent ACS risk in the following 6 months.<sup>29</sup> The Charlson comorbidity index was used as an estimate of low, medium, or high 10-year mortality risk.<sup>30</sup> Self-rated health with reference to the time before ACS was assessed with the EuroQol Visual Analogue Scale (<https://euroqol.org/euroqol/>), ranging from 0 (“worst imaginable health state”) to 100 (“best imaginable health state”).<sup>31</sup> For information on lifetime depression, patients were asked the question, “Have you ever had a depression in your life? (yes/no).” We used the 19-item self-rating Acute Stress Disorder Scale to measure acute stress disorder (ASD) symptoms of dissociation, reexperiencing, avoidance, and arousal, which had occurred “since the heart attack.”<sup>32</sup> Each item is rated on a 5-point Likert scale (0 indicates “not at all”; and 4, “extremely”; total severity score, 0–76). In patients who completed all items, the Cronbach  $\alpha$

for the scale was 0.83. We measured negative mood with the Global Mood Scale,<sup>33</sup> asking participants to rate the extent to which they felt each of 10 mood states “at the moment” on a 5-point Likert Scale (0 indicates “not at all”; and 4, “extremely”; total severity scale, 0–40). Typical items are “fatigued,” “insecure,” and “helpless.” In patients who completed all items, the Cronbach  $\alpha$  for the scale was 0.85.

## Assessment and Classification of PTSS

Three months after ACS, we assessed ACS-induced PTSS with the Clinician-Administered PTSD Scale (CAPS) on the basis of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*, criteria.<sup>34</sup> Trained interviewers, blinded to the intervention assignment, rated the frequency and intensity of each of the 17 PTSS, referring to the prior month between 0 (“never”) and 4 (“almost always”); the total PTSS severity score is 0 to 136. As an indication of the clinical relevance of PTSS, we additionally classified patients as “full PTSD,” “subsyndromal PTSD,” or “non-PTSD” on the basis of whether they met criteria for the presence or absence of symptom clusters.<sup>35</sup> One of 5 symptoms is required for the reexperiencing cluster, 3 of 7 symptoms are required for the avoidance/numbing cluster, and 2 of 5 symptoms are required for the hyperarousal cluster. Patients who met criteria for all 3 symptom clusters were diagnosed with full PTSD. Patients who met criteria for the reexperiencing cluster and either the avoidance/numbing or the hyperarousal cluster were diagnosed with subsyndromal PTSD. Patients who met full or subsyndromal criteria for PTSD were lumped together and defined as patients with “clinical PTSD.” Patients who met criteria for either one or no symptom cluster were non-PTSD cases. The Cronbach  $\alpha$  was 0.79 for the CAPS total scale, 0.68 for the reexperiencing scale, 0.66 for the avoidance/numbing scale, and 0.44 for the hyperarousal scale, indicating moderate-to-good internal consistency, except for the hyperarousal scale.

## Statistical Analysis

Data were analyzed using SPSS 26.0 for Windows (SPSS Inc, Chicago, IL) with 2-tailed significance of  $P < 0.05$ . We used multiple imputation to replace missing values, applying the default method “automatic.” This imputation method scans the data to determine the best imputation method (fully conditional specification or monotone). The following variables were used for the imputation model: STEMI, age, sex, education, GRACE score, Charlson comorbidity index, self-rated health, depression history, pain during MI, fear of dying during MI, ASD symptoms, negative mood, all drugs, and all CAPS scores. Five imputations were performed, as the percentage of

missing values across all variables in the analysis was only 3.6% (111 of totally 2969 values missing). Specifically, missing values were  $n=1$  for index MI, education, and antidepressants;  $n=3$  for lifetime depression history;  $n=4$  for  $\beta$ -blockers;  $n=5$  for benzodiazepine and morphine use;  $n=12$  for GRACE score;  $n=25$  for ASD Scale score;  $n=26$  for self-rated health; and  $n=28$  for negative mood. The Little Missing Completely at Random test indicated that quantitative variables were completely missing at random ( $P=0.39$ ). Nonnormal variables were not transformed before the imputation. However, after imputation, for further analyses, CAPS, GRACE, and ASD Scale scores were square root transformed to approximate a more normal distribution. There were no significant differences in CAPS scores and the proportion of benzodiazepine, morphine,  $\beta$ -blocker, and antidepressant use between participants with ( $n=114$ ) and those without ( $n=40$ ) complete data (all  $P>0.27$ ).

We used independent-sample  $t$ -test or  $\chi^2$  test to determine group differences in parametric and nonparametric variables, respectively, and the Kendall  $\tau$ -b to estimate the correlation between drug exposure and patient characteristics. We performed univariable and multivariable linear regression analyses to determine associations of drug exposure with the CAPS total severity score (primary outcome) and the scores of the 3 PTSS clusters (secondary outcomes). For the multivariable analyses, covariates were selected on the basis of the literature on risk factors for cardiac disease-induced PTSS and associations of  $\beta$ -blocker or benzodiazepine exposure with the development of PTSS in trauma survivors.<sup>13,24,36</sup> To avoid overfitting, we limited the number of predictors to 15 (11 covariates and 4 drugs). We considered demographics (sex, age, and education), clinical variables (GRACE score, Charlson comorbidity index, and self-rated health), and psychological measures (pain and fear of dying during ACS, depression history, ASD symptoms, and negative mood). For a complementary analysis, we used logistic regression to estimate the relative risk of developing clinical PTSD with drug exposure, adjusting for covariates, which were significant and independent predictors of the CAPS total score in the linear regression model. Regression output revealed no influential outliers or concern for multicollinearity in the set of predictor variables.

## RESULTS

### Patient Characteristics

Three months after ACS, 1 patient was diagnosed with full PTSD and 17 patients were diagnosed with subsyndromal PTSD, bringing the total number of patients diagnosed with clinical PTSD to 18,

a prevalence of 11.7%. Table 1 shows the baseline characteristics and CAPS scores at 3 months of the 154 study participants as a whole group and in a group comparison between patients with versus without clinical PTSD. Most of the study participants were men, were well educated, and showed rather low medical comorbidity. The vast majority were treated in the coronary care unit with opioids (morphine in all cases) and  $\beta$ -blockers (metoprolol in  $\approx 90\%$  of cases). Slightly more than a third received benzodiazepines (lorazepam in  $\approx 80\%$  of cases). Three patients reported current use of benzodiazepines before the ACS, 1 in the group with clinical PTSD and 2 in the group with no PTSD; all 3 also received a benzodiazepine during ACS. A total of 45 (29.2%) patients reported having had depression in the past, and only 11 (7.1%) patients reported current use of antidepressants. Compared with those without clinical PTSD, patients with clinical PTSD were significantly younger, were more often diagnosed with STEMI than non-ST-segment-elevation MI, and had more severe negative mood and, as expected, more severe PTSS. Patients with clinical PTSD were also more frequently exposed to benzodiazepines, although not morphine,  $\beta$ -blockers, or antidepressants, than those without clinical PTSD. The study sample characteristics stratified by benzodiazepine use are shown in Table 2.

### Associations Between Drug Exposure and Baseline Characteristics of Patients

There were several zero-order correlations between drug exposure at admission and patients' baseline characteristics. The use of benzodiazepine was associated with increased fear of dying ( $r=0.16$ ;  $P=0.048$ ) and increased negative mood ( $r=0.24$ ;  $P=0.002$ ). Morphine administration was associated with STEMI ( $r=0.18$ ;  $P=0.025$ ) and increased fear of dying ( $r=0.19$ ;  $P=0.021$ ). Administration of  $\beta$ -blockers was associated with STEMI ( $r=0.39$ ;  $P<0.001$ ) and a higher Charlson comorbidity index ( $r=0.17$ ;  $P=0.043$ ). Exposure to antidepressants was associated with lower self-rated health ( $r=-0.22$ ;  $P=0.009$ ), depression history ( $r=0.16$ ;  $P=0.046$ ), and increased negative mood ( $r=0.18$ ;  $P=0.042$ ).

### Association Between Drug Exposure and PTSS After 3 Months

#### Total PTSS Severity

The regressions of the CAPS total severity score on drug use at admission, subsequently adjusted for blocks of covariates, are summarized in Table 3. The use of benzodiazepine was significantly associated with a higher CAPS total score in all models. Partial



**Table 1. Characteristics of All Study Participants and Between Groups With and Without Clinical PTSD**

Variable	All (n=154)	Clinical PTSD (n=18)	No PTSD (n=136)	P Value
Age, mean (SD), y	58.7 (10.9)	53.8 (9.5)	59.4 (10.9)	0.039
Male sex, n (%)	130 (84.4)	16 (88.9)	114 (87.7)	0.741
Educational level, n (%)				
High/medium/low	29 (18.8)/114 (74.0)/11 (7.2)	0 (0)/17 (94.4)/1 (5.6)	29 (21.3)/97 (71.3)/10 (7.4)	0.078
ST-segment-elevation MI, n (%)	110 (71.4)	17 (94.4)	93 (68.4)	0.022
GRACE score, median (IQR)	102.5 (84.7–118.4)	95.7 (84.2–121.3)	102.7 (84.7–118.0)	0.884
Charlson comorbidity index, n (%)				
Low/medium/high	88 (57.2)/39 (25.3)/27 (17.5)	12 (66.7)/4 (22.2)/2 (11.1)	76 (55.9)/35 (25.7)/25 (18.4)	0.644
Self-rated health, mean (SD)	73.5 (17.4)	68.6 (24.7)	74.1 (18.5)	0.352
Depression history (yes), n (%)	45 (29.2)	8 (44.4)	37 (27.2)	0.135
Pain score, mean (SD)	7.9 (1.6)	7.8 (1.7)	7.9 (1.6)	0.553
Fear of dying score, mean (SD)	5.1 (2.9)	6.2 (2.8)	4.9 (2.9)	0.072
ASD symptoms, median (IQR)	16.2 (9.2–23.0)	17.8 (11.0–27.0)	15.3 (9.0–23.0)	0.388
Negative mood, mean (SD)	14.2 (6.8)	17.4 (4.5)	13.8 (6.9)	0.012
Benzodiazepine, n (%)	58 (37.7)	12 (66.7)	46 (33.8)	0.007
Morphine, n (%)	111 (72.1)	13 (72.2)	98 (72.1)	0.936
β-Blocker, n (%)	136 (88.3)	18 (100)	118 (86.8)	0.168
Antidepressant, n (%)	11 (7.1)	3 (16.7)	8 (5.9)	0.198
CAPS scores, median (IQR)				
Total symptom severity	8 (3.0–15.0)	27.5 (23.0–39.8)	6.5 (2.0–11.8)	<0.001
Reexperiencing symptoms	2 (0–3.3)	11.0 (9.0–13.0)	0 (0–2.0)	<0.001
Avoidance/numbing symptoms	2 (0–4.0)	7.5 (2.0–13.5)	1.5 (0–3.0)	<0.001
Hyperarousal symptoms	4 (2.0–7.3)	12.0 (9.3–16.0)	4.0 (2.0–6.0)	<0.001

The category "Clinical PTSD" includes 1 patient with full PTSD and 17 patients with subsyndromal PTSD. ASD indicates acute stress disorder; CAPS, Clinician-Administered PTSD Scale; GRACE, Global Registry of Acute Coronary Events; IQR, interquartile range; MI, myocardial infarction; and PTSD, posttraumatic stress disorder.

correlation coefficients  $r$  for the association between benzodiazepine use and the CAPS total score ranged between 0.18 (fully covariate-adjusted model 5) and 0.25 (model 4, adjusted for the other drugs and demographic and clinical variables), suggesting small, but clinically significant, effects. The results for the CAPS total severity score did not change when the 3 participants who had received a benzodiazepine before ACS were excluded from the analysis (fully covariate-adjusted model 5: B [SE], 0.632 [0.276]; partial  $r=0.20$ ;  $P=0.022$ ). In contrast to benzodiazepine exposure, exposure to morphine, β-blockers, or antidepressants during MI showed no significant association with the CAPS total score at 3 months in any model.

### Individual PTSS Clusters

In the univariable model, benzodiazepine use was significantly associated with both CAPS reexperiencing (B [SE], 0.547 [0.204]; partial  $r=0.22$ ;  $P=0.008$ ) and avoidance/numbing (B [SE], 0.512 [0.202]; partial  $r=0.20$ ;  $P=0.011$ ) scores, but not hyperarousal scores ( $P=0.21$ ) after 3 months. Benzodiazepine use

remained significantly associated with reexperiencing (B [SE], 0.433 [0.217]; partial  $r=0.17$ ;  $P=0.047$ ) but not avoidance/numbing ( $P=0.098$ ) scores, after adjusting for exposure to morphine, β-blockers, and antidepressants, age, sex, education, GRACE score, Charlson comorbidity index, self-rated health, depression history, pain and fear of dying during MI, ASD symptoms, and negative mood. The result for reexperiencing symptoms was maintained in the fully covariate-adjusted model, when the 3 participants who had received a benzodiazepine before ACS were excluded from the analysis (B [SE], 0.489 [0.216]; partial  $r=0.20$ ;  $P=0.024$ ). There were no significant associations of morphine, β-blocker, or antidepressant exposure during MI with any of the 3 CAPS symptom clusters at 3 months, both in univariable and fully adjusted multivariable analyses (statistics not shown).

### Associations Between Covariates and PTSS After 3 Months

In the univariable analysis, shown in Table 2, there were several baseline demographic factors, clinical

**Table 2. Characteristics of All Study Participants, Stratified by Benzodiazepine Use**

Variable	Benzodiazepine Use (n=58)	No Benzodiazepines (n=96)
Age, mean (SD), y	58.3 (11.0)	58.9 (11.8)
Male sex, n (%)	51 (82.3)	79 (87.9)
Educational level, n (%)		
High/medium/low	9 (15.5)/48 (82.8)/1 (1.7)	20 (20.8)/66 (68.8)/10 (10.4)
ST-segment-elevation MI, n (%)	47 (81.0)	64 (66.7)
GRACE score, median (IQR)	105.2 (86.8–121.5)	101.5 (84.0–114.2)
Charlson index, n (%)		
Low/medium/high	33 (56.9)/17 (29.3)/8 (13.8)	55 (57.3)/22 (22.9)/19 (19.8)
Self-rated health, mean (SD)	76.1 (17.8)	71.9 (20.0)
Depression history (yes), n (%)	13 (22.4)	32 (33.3)
Pain score, mean (SD)	8.0 (1.8)	7.8 (1.5)
Fear of dying score, mean (SD)	5.7 (3.2)	4.7 (2.7)
ASD symptoms, median (IQR)	20.4 (11.9–25.2)	13.9 (9.2–22.0)
Negative mood, mean (SD)	16.9 (6.5)	12.6 (7.4)
Morphine, n (%)	45 (77.6)	66 (68.8)
β-Blocker, n (%)	52 (89.7)	84 (87.5)
Antidepressant, n (%)	3 (5.2)	8 (8.3)
Clinical PTSD, n (%)	12 (20.7)	6 (6.3)
CAPS scores, median (IQR)		
Total symptom severity	9.6 (4.0–22.0)	7.0 (2.2–12.0)
Reexperiencing symptoms	2.0 (0–6.1)	0 (0–3.0)
Avoidance/numbing symptoms	2.0 (0–6.0)	1.9 (0–3.0)
Hyperarousal symptoms	5.1 (2.0–8.0)	4.0 (2.0–7.0)

The category "Clinical PTSD" includes 1 patient with full PTSD and 17 patients with subsyndromal PTSD. ASD indicates acute stress disorder; CAPS, Clinician-Administered PTSD Scale; GRACE, Global Registry of Acute Coronary Events; IQR, interquartile range; MI, myocardial infarction; and PTSD, posttraumatic stress disorder.

variables, and psychological measures, which were significantly associated with the CAPS total severity score after 3 months. Younger patients and those with lower self-rated health, a history of depression, greater fear of dying during MI, more severe ASD symptoms, and negative mood showed a higher CAPS total score at 3 months. However, in the fully adjusted model 5, only ASD symptoms emerged as a significant and independent predictor of the CAPS total score. Moreover, adjusting for all covariates, there were independent associations of ASD symptoms with CAPS reexperiencing (B [SE], 0.186 [0.078];  $P=0.017$ ), avoidance/numbing (B [SE], 0.196 [0.082];  $P=0.017$ ), and hyperarousal (B [SE], 0.210 [0.078];  $P=0.007$ ) scores, and of higher education with lower reexperiencing scores (B [SE],  $-0.629$  [0.191];  $P=0.001$ ).

### Association Between Drug Exposure and Clinical PTSD

As all participants with clinical PTSD had received β-blockers, odds ratios (ORs) could only be calculated for benzodiazepine, morphine, and antidepressant exposure. Patients with benzodiazepine use had

an almost 4-fold increased risk of developing clinical PTSD relative to patients who did not receive a benzodiazepine (OR, 3.89; 95% CI, 1.37–11.04). This result changed little with additional adjustment for ASD symptoms (OR, 3.75; 95% CI, 1.31–10.77) or exposure to morphine and antidepressants (OR, 4.31; 95% CI, 1.46–12.74). In contrast, exposure to morphine (OR, 1.02; 95% CI, 0.34–3.09) or antidepressants (OR, 3.39; 95% CI, 0.79–14.43) was not significantly associated with an increased risk of developing clinical PTSD; these results did not change with additional adjustment for ASD symptoms. The detailed logistic linear regression models for these analyses are presented in Table S1.

## DISCUSSION

As a novelty, the main finding of our study was that patients who received a benzodiazepine within hours of acute MI had more severe PTSS 3 months later compared with patients not exposed to a benzodiazepine. This association was robust with adjustment for the effects of exposure to morphine and β-blockers, current use of antidepressants, and a range of previously

**Table 3. Univariable and Multivariable Linear Associations Between Drug Use at Admission and Total PTSS Severity 3 Months After MI**

Variables Entered	Model 1		Model 2		Model 3		Model 4		Model 5	
	B (SE)	P Value	B (SE)	P Value	B (SE)	P Value	B (SE)	P Value	B (SE)	P Value
Benzodiazepine use	0.688 (0.268)	0.010	0.694 (0.271)	0.011	0.721 (0.266)	0.007	0.805 (0.266)	0.003	0.589 (0.274)	0.032
Morphine use	−0.037 (0.298)	0.902	−0.154 (0.309)	0.618	−0.173 (0.307)	0.574	−0.103 (0.299)	0.730	−0.072 (0.296)	0.809
β-Blocker use	0.314 (0.418)	0.453	0.336 (0.423)	0.427	0.481 (0.418)	0.250	0.589 (0.432)	0.173	0.582 (0.421)	0.167
Antidepressant use	−0.084 (0.551)	0.878	−0.064 (0.552)	0.908	−0.131 (0.542)	0.809	−0.641 (0.556)	0.250	−0.578 (0.530)	0.275
Age	−0.025 (0.012)	0.038			−0.026 (0.012)	0.029	−0.035 (0.016)	0.034	−0.025 (0.016)	0.129
Male sex	−0.480 (0.363)	0.186			−0.616 (0.357)	0.084	−0.579 (0.351)	0.099	−0.488 (0.344)	0.155
High education	−0.311 (0.266)	0.242			−0.397 (0.262)	0.130	−0.457 (0.258)	0.077	−0.456 (0.251)	0.069
GRACE score	−0.075 (0.103)	0.471					0.036 (0.144)	0.800	−0.030 (0.142)	0.835
Charlson comorbidity index	0.051 (0.172)	0.293					0.050 (0.177)	0.779	0.086 (0.166)	0.606
Self-rated health	−0.019 (0.008)	0.016					−0.027 (0.008)	0.001	−0.015 (0.009)	0.098
Depression history	0.635 (0.287)	0.027							0.328 (0.310)	0.291
Pain during MI	−0.051 (0.081)	0.530							−0.109 (0.077)	0.157
Fear of dying during MI	0.130 (0.044)	0.003							0.041 (0.046)	0.380
ASD symptoms	0.460 (0.091)	<0.001							0.325 (0.101)	0.001
Negative mood	0.070 (0.020)	0.001							0.016 (0.022)	0.468

Results are shown for square root-transformed PTSS scores. Model 1, univariable associations with PTSS. Model 2, drugs entered in one block. Model 3, drug effects adjusted for demographics. Model 4, model 3 plus additional adjustment for clinical variables. Model 5, model 4 plus additional adjustment for psychological variables. ASD indicates acute stress disorder; GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction; and PTSS, posttraumatic stress disorder symptoms.

identified risk factors for cardiac disease–induced PTSS.<sup>13</sup> The magnitude of this association was clinically significant. In a complementary analysis, we found an almost 4-fold increased relative risk of clinical PTSD (full and subsyndromal PTSD combined) in patients with benzodiazepine exposure during MI. To the extent that CIs were wide and the number of 18 patients with a diagnosis of clinical PTSD allowed statistical adjustment for few variables only, this result must be interpreted carefully. Nonetheless, the prevalence of 11.7% of clinical PTSD in our sample corresponds well to the prevalence of 12% (95% CI, 9%–16%) for clinically significant ACS-induced PTSS in a previous meta-analysis.<sup>14</sup> Therefore, the distribution of CAPS scores permitted us to find clinically significant effects of benzodiazepine use on ACS-induced PTSS, not only along a continuum of PTSS severity, but also with clinical relevance. Furthermore, for the development of ACS-induced PTSS, the effects of benzodiazepines could be at least as important as those of known risk factors. Younger age and several psychological variables correlated significantly with the CAPS total severity score, but benzodiazepine use emerged as the only significant predictor besides ASD symptoms in the fully adjusted model.

Our observation that administration of a benzodiazepine during ACS is associated with increased PTSS is consistent with meta-analytic data from other study populations suggesting that benzodiazepines may significantly increase the risk of developing PTSD when used after recent trauma.<sup>16,17</sup> For instance, in one study, adults on mechanical ventilation and sedated with midazolam showed clinically significant PTSS 2 months later.<sup>37</sup> In another study, the total dose of lorazepam that mechanically ventilated patients received during the intensive care unit stay was associated with PTSS severity 6 months after discharge.<sup>38</sup> On the basis of clinical and experimental studies, benzodiazepines could interfere with relearning in the recovery from trauma, increasing patients' vulnerability to react with posttraumatic behaviors at times of stress and trauma-related cues.<sup>17</sup> Inhibited adaptation to trauma-related memories<sup>39</sup> could explain our observation of a significant and independent association of benzodiazepine use during ACS with reexperiencing symptoms, but not with avoidance/numbing and hyperarousal symptoms. We could not confirm earlier assumptions that the association of benzodiazepine use with PTSS could simply reflect the fact that patients with increased peritraumatic anxiety<sup>16</sup> or ASD<sup>38</sup> are more likely to receive benzodiazepines, as we controlled in our analyses for fear of dying and ASD symptoms. However, there might be other reasons for confounding by indication (ie, the types of patients who clinicians believe could benefit from benzodiazepines could be exactly those patients who are more likely to

develop PTSS after ACS, regardless of exposure to a benzodiazepine).

Our findings on benzodiazepine use as a potential risk factor for ACS-induced PTSS should not discount the short-term antianxiety and pain-alleviating effects of benzodiazepines. In addition, benzodiazepines may have beneficial cardiovascular effects, directly or indirectly, via anxiety reduction; these include vasodilation, anti-ischemic and antiarrhythmic properties, platelet inhibition, and lowering of catecholamine levels.<sup>10</sup> A potential alternative to benzodiazepine treatment is reassurance of anxious patients admitted with ACS and their significant others.<sup>6</sup> Unfortunately, this recommendation is often not sufficiently implemented in everyday clinical practice because of time constraints and lack of awareness. Moreover, in a previous study, non-pharmacological management of anxiety by clinicians was not associated with a reduction in anxiety levels in patients admitted with ACS, whereas pharmacological management showed an effect.<sup>3</sup> Still, clinicians should be aware that ACS-induced PTSS have been associated with an increased risk of recurrent cardiac events and all-cause mortality.<sup>14</sup> Therefore, in patients who are candidates for benzodiazepines, the search for effective and early behavioral in-hospital interventions to prevent ACS-induced PTSS could particularly be justified.<sup>40</sup> Targeted means, such as avoiding emergency department crowding,<sup>41</sup> could also counteract potentially adverse effects of benzodiazepine use on the development of ACS-induced PTSS.

We further found that, in contrast to benzodiazepine exposure during ACS, exposure to morphine and  $\beta$ -blockers and current use of antidepressants was not significantly associated with the development of PTSS. This is consistent with the available evidence from randomized controlled trials on early pharmacotherapy in survivors of noncardiac trauma.<sup>22,23,42</sup> However, such studies are rare, precluding meta-analysis on effects of morphine,<sup>42</sup> which reduced PTSD incidence in civilian and military patients,<sup>18,19</sup> but may delay onset of action of oral antiplatelet agents in patients with ACS.<sup>43</sup> In addition, only propranolol was tested,<sup>23</sup> a lipophilic and nonselective  $\beta$ -blocker, able to cross the blood-brain barrier and to block traumatic memory consolidation,<sup>44</sup> but not administered during ACS. Interestingly, metoprolol, which is also lipophilic but a selective  $\beta_1$ -adrenoreceptor antagonist, was previously suggested to have fear-reducing properties after trauma.<sup>45</sup> In a previous study, patients exposed to  $\beta$ -blockers during emergency department evaluation for ACS had less severe PTSS at 1 month, although not the subgroup with confirmed ACS, and, unfortunately, the types of used  $\beta$ -blockers were unknown.<sup>24</sup> Previous trials with escitalopram were not prevention, but early treatment, trials,<sup>46,47</sup> and our patients were taking antidepressants yet before MI, pointing to the



vulnerable health of this small subgroup. Specifically, current use of antidepressants was associated with a history of lifetime depression, poorer self-rated health, and negative mood. The rate of almost 30% of preexisting depression in our study participants is consistent with other cardiovascular literature.<sup>48</sup> The low number of patients with current use of antidepressants, and the high number exposed to morphine and metoprolol during ACS as well, made it difficult to find a significant group difference for the development of PTSS. Clearly, we would need randomized controlled trials to demonstrate potentially preventive effects of early pharmacotherapy on the development of ACS-induced PTSS if cardiovascular adverse effects of drug candidates will not prohibit this.

Our study yielded further results with potential clinical relevance. In accordance with guidelines for the pharmacological management of patients with STEMI,<sup>6</sup> we observed more frequent morphine and  $\beta$ -blocker use in STEMI than non-ST-segment-elevation MI, and increased fear of dying in the 38% of patients who received a benzodiazepine. Chest pain can augment anxiety,<sup>10</sup> a possible explanation for why fear of dying was associated with morphine use in our patients. In contrast, pain intensity was not associated with any drug, but this could be a result of our study design. Patients were eligible to participate when they had increased pain during MI, for which the vast majority received morphine treatment. This could have masked an association between pain scores and morphine use. The same could apply to metoprolol, previously shown to reduce pain,<sup>11</sup> which was administered in about 90% of our patients. The variance in fear of dying scores was wider, which may have helped to reveal significant associations with morphine and benzodiazepine use. These interpretations must consider that fear of dying and pain, but also negative mood, were assessed several hours after drug administration, precluding causal inferences. As negative mood was significantly elevated in patients who had received a benzodiazepine, the benzodiazepine could have induced negative mood, but the latter could also have augmented self-reports on fear of dying in patients' retrospect.

The assessment of PTSS with a clinical interview and of a range of potentially important confounding variables were strengths of our study, which also had its limitations. The findings are based on a secondary analysis of data collected from patients with elevated levels of pain and fear of dying who participated in a behavioral intervention trial. The association between benzodiazepine use and PTSS is purely observational, was at the lower end of a clinically important effect size, and does not prove causality. Particularly, it is possible that the same patient characteristics that lead to PTSS lead to prescribing a benzodiazepine in the setting of

an acute MI. Precise information on the dosage and time of administration of drugs was not available. The sample size precluded inclusion of further covariates in statistical models, including health behaviors, so residual confounding remains a possibility. Our results may not be transferable to populations of patients with ACS who have less peritraumatic distress but greater diversity in terms of sociodemographic characteristics and medical comorbidity. In particular, the low proportion of female patients did not allow a stratified analysis by sex. The null findings on hyperarousal symptoms must be interpreted with caution because of the poor reliability of the scale, and whether results would hold with the new *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* criteria for PTSD is unclear.

Taken together, we found that benzodiazepine exposure during ACS was associated with increased MI-induced PTSS severity after 3 months. No such effects were observed for exposure to morphine, exposure to  $\beta$ -blockers, and current use of antidepressants during ACS.

## ARTICLE INFORMATION

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### Disclosures

None.

### Supplementary Material

Table S1

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# **SUPPLEMENTAL MATERIAL**



**Table S1. Univariable and multivariable binary logistic regression analyses for the risk of clinical PTSD 3 months after MI with drug use at hospital admission.**

Variables entered	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Model 1						
Benzodiazepine use	3.89 (1.37, 11.04)	.011				
Morphine use			1.02 (0.34, 3.09)	.969		
Antidepressant use					3.39 (0.79, 14.43)	.099
Model 2						
Benzodiazepine use	3.75 (1.31, 10.77)	.014				
Morphine use			1.03 (0.34, 3.13)	.956		
Antidepressant use					3.51 (0.82, 15.10)	.092
ASD symptoms	1.11 (0.75, 1.64)		1.19 (0.81, 1.74)	.387	1.20 (0.82, 1.77)	.354
Model 3						
Benzodiazepine use	4.31 (1.46, 12.74)	.008				
Morphine use	1.03 (0.32, 3.37)	.906				
Antidepressant use	4.48 (0.93, 21.66)	.062				

ASD, acute stress disorder; PTSD, posttraumatic stress disorder. ASD scores were square-root transformed. Model 1: univariable associations of each drug with clinical PTSD. Model 2: each drug entered with ASD symptoms in one block. Model 3: all three drugs entered in one block.